Amyotrophic Lateral Sclerosis Among Veterans Deployed in Support of Post-9/11 U.S. Conflicts

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ABSTRACT

Introduction

Amyotrophic lateral sclerosis (ALS) is a recognized military service-connected condition. Prior prevalence studies of ALS among U.S. war Veterans were not able to address concerns related to neurodegenerative sequelae of traumatic brain injury (TBI) and disregarded risk heterogeneity from occupational categories within service branches.

Materials and Methods

We identified the prevalence of definite and possible ALS and cumulative incidence of definite ALS among Post-9/11 U.S. Veterans deployed in support of Post-9/11 conflicts (mean age 36.3) who received care in the Veterans Health Administration during fiscal years 2002–2015. Using a case-control study design, we also evaluated the association of TBI and major military occupation groups with ALS adjusting for demographics and comorbidities.

Results

The prevalence of ALS was 19.7 per 100,000 over 14 years. Both prevalence and cumulative incidence of definite ALS were significantly higher among Air Force personnel compared to other service branches and among tactical operation officers and health care workers compared to general and administrative officers. Neither TBI nor younger age (<45 years) was associated with ALS. Depression, cardiac disease, cerebrovascular disease, high blood pressure, and obstructive sleep apnea were clinical comorbidities significantly associated with ALS in this population of Veterans.

Conclusion

This study among a cohort of relatively young Veterans showed a high ALS prevalence, suggesting an early onset of ALS among deployed military service members. The higher prevalence among some military specific occupations highlights the need to determine which occupational exposures specific to these occupations (particularly, Air Force personnel, tactical operations officers, and health care workers) might be associated with early onset ALS.

INTRODUCTION

U.S. military service has been recognized as being a risk factor for amyotrophic lateral sclerosis (ALS) among studies in Gulf War Veterans (GWV) and among Veterans from previous wars.[1–5] Average annual cumulative incidence of ALS among GWV was 0.43 per 100,000 persons, with a case rate of 6.7 per million among the deployed compared to 3.5 per million among nondeployed. Recent studies using National Registry of Veterans with ALS, Genes and Environmental Exposures in Veterans with ALS (GENEVA) cohort, and participants of the National Longitudinal Mortality study are also mostly limited to those served in Gulf War and prior and include only a small sample of participants who served in the Post-9/11 U.S. wars in Iraq and Afghanistan.[6–8] Post-9/11 war Veterans do differ with other war era Veterans in terms of age, injury severity, disability, and survival, in addition to unique occupational exposures which may result in excess risk for ALS. However, no research on the occurrence of and factors associated with ALS specific to Post-9/11 deployed U.S. war Veterans has been conducted.

Some evidence suggests that even a single traumatic brain injury (TBI) can precipitate or accelerate age-related neurodegeneration and has been considered a possible trigger of ALS.[9–11] Chen et al.,[10] reported a threefold increased risk of ALS (odds ratio [OR] 3.2; 95% confidence interval [CI] 1.0–10.2) among those with a history of TBI compared to those without TBI. Schmidt et al. found that, among the

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The views expressed are solely those of the authors and do not reflect the official policy or position of the Department of Veterans Affairs.

doi:10.1093/milmed/usz350

GENEVA study cohort (which primarily consisted of pre-9/11 war Veterans), those who reported a history of head injuries had significantly higher odds of ALS relative to those without head injury (OR:2.3 [95% CI 1.2–4.6]).[12] Given the relatively high prevalence of TBI among Post-9/11 deployed U.S. war Veterans,[13] it is important to examine the association of TBI with ALS in this population.

While military service is associated with ALS in U.S. Veterans, no specific characteristic of military service (eg, combat, place of deployment, service branch) has been consistently associated with ALS.[14] Studies among GWV reported higher prevalence of ALS in Air Force personnel than in other branches.[3,5] However, recent studies, which also included pre-Gulf War era Veterans, reported that the odds of ALS did not differ by branch.[6] Studying military branches, however, disregards the heterogeneity of within-branch populations with high exposure variability by job type (such as variations in the exposures to radiation, chemicals, or traumatic events).[5,15]

The goals of this study are to identify the prevalence of ALS among deployed Post-9/11 U.S. war Veterans and determine if certain patient characteristics, such as TBI or military branch or occupation, are associated with risk for ALS controlling for comorbid conditions previously associated with ALS (metabolic disorders such as diabetes and dyslipidemia, cancer, cardiac and cerebrovascular diseases) and comorbid conditions common in this population [such as post-traumatic stress disorder (PTSD), depression, anxiety, etc.]. We used standardized occupational category codes to classify the study population into clearly defined job groups and thus can subsequently provide the basis to study risk by job or infer exposure to specific agents. Results will enhance our understanding of occupational exposures and the ability of the Veterans Health Administration (VHA) to plan the resource needs that best address the complex service needs of these disabled Veterans cared for in VHA.

METHODS

Study Population

Using roster data of individuals deployed in support of Post-9/11 U.S. operations, we identified 1,149,620 Veterans who received care in the VHA between October 1, 2001 and September 30, 2015 (fiscal year FY2002–FY2015). We used VHA inpatient, outpatient, pharmacy data, and Veterans Benefits Administration (VBA) data to identify potential cases of ALS. This study was approved by Institutional Review Boards at the University of Utah, the University of Texas Health Science Center San Antonio, the Bedford VA Medical Center, and the Department of Defense Human Research Protection Office.

Case Definitions

The study population was categorized into ALS cases and no ALS based on the Agency for Toxic Substances and Disease Registry's (ATSDR) updated algorithm (see Supplementary Table S1).[16] "Definite ALS" cases had a record of an International Classification of Diseases, 9th Revision [ICD-9] diagnostic code of 335.20 in at least one data year (ie, 2001–2015) with a combination of either a prescription for riluzole, a VBA 8017 code (indicating that the veteran is considered disabled due to ALS), or one or more neurology visits in the same data source (VHA data). A "possible ALS" case had only the VBA code. A case of "other ALS" was one with the ICD-9 code of 335.20 in only one data year but fewer than five neurology visits in the same data source. The rest of the individuals were classified as "no indication of ALS."

Study Design

We used a case-control study design to examine the extent to which various military occupations and exposure to TBI increase risk for ALS. The study cohort is relatively young with only a small number of ALS cases and without definitive data regarding age or date of diagnosis. Hence, we first identified the definite or possible ALS cases and then considered those with "no indication of ALS" as study controls.

Study Measures

Traumatic Brain Injury

We used a previously validated algorithm among Veterans, which takes into account both clinical and diagnostic information from various available Department of Defense (DoD) and VHA data sources to identify TBI status (Yes/No) for each individual in the study. This algorithm uses all available data with the data most proximal to the injury having the highest priority in the following order: DoD Trauma Registry (Glasgow Coma Scale), DoD, and VA health system data ICD-9 codes.[17,18]

Military Occupational Characteristics

Roster data provided information on military status including Military Occupational Specialty (MOS) codes, component of service (active duty vs. National Guard/Reserve), branch of service (Army, Air Force, Navy/Coast Guard, and Marines), and rank (enlisted vs. officer/warrant officer). Using a military crosswalk obtained from the workforce information database,[19] MOS codes were matched based on the branch of service and rank to their respective DoD occupational codes to obtain the study occupational categories (see Supplementary Table S2).

Covariates

VHA inpatient and outpatient data were used to identify age on entry to VA (grouped into <45 years and ≥ 45 years), sex, and race/ethnicity and provide information on clinical conditions for which care was received during the study period. Comorbid conditions were identified for FY02-FY15 using ICD-9-CM codes and use of medications. As the timeline for the diagnosis of these conditions (ie, prior to ALS diagnosis

TABLE I. Sample Characteristics by Study Group

	No ALS (%)	Definite ALS *n* (%)	Definite ALS vs. No ALS Chi-Square *P*-Value	Possible ALS *n* (%)	Possible ALS vs. No ALS Chi-Square *P*-Value
Total (*N*)	1,149,374	139		87	
Demographics					
Age at entry to VHA [Mean (SD)]	31.7 (9.1)	39.7 (9.8)	<0.001	36.3(10.6)	<0.001
Male	87.6%	96.4% (134)	0.002	89.7% (78)	0.566
Race/ethnicity					
Black	16.1%	15.1% (21)	0.019	14.9% (13)	0.932
Hispanic	11.0%	7.9% (11)		(<12.0%)[a]	
Other	7.3%	(<2.0%)[a]		(<6.0%)[a]	
White	65.6%	75.5% (105)		67.8% (59)	
Rank					
Officer/Warrant	9.2%	22.3% (31)	<0.001	13.8% (12)	0.142
Enlisted	90.8%	77.7% (108)		86.2% (75)	
Branch of service					
Air Force	13.4%	24.5% (34)	<0.001	19.5% (17)	0.230
Marines	13.9%	(<3.0%)[a]		(<4.0%)[a]	
Navy/Coast Guards	14.2%	15.1% (21)		16.1% (14)	
Army	58.6%	57.6% (80)		60.9% (53)	
Status					
Reserve/Guard	37.1%	49.7% (69)	0.002	42.5% (37)	0.293
Active Duty	62.9%	50.4% (70)		57.5% (50)	
Education					
High school	76.9%	57.6% (80)	<0.001	72.4% (63)	0.354
Some college	21.9%	41.0% (57)		(<10.0%)[a]	
Unknown	1.4%	(<2.0%)[a]		(<3.0%)[a]	
Comorbidities					
TBI	*20.1%*	*20.1% (28)*	*0.980*	*24.1% (21)*	*0.349*
Mental health					
Depression	23.9%	36.7% (51)	<0.001	33.3% (29)	0.038
PTSD	28.4%	27.3% (38)	0.779	35.6% (31)	0.135
Nicotine dependence	25.9%	29.5% (41)	0.338	27.6% (24)	0.725
Other conditions					
Cancer	0.9%	(<6.0%)[a]	<0.001	(<3.0%)[a]	0.180
Diabetes	3.0%	(<8.0%)[a]	<0.001	(<5.0%)[a]	0.338
Obesity	12.6%	9.4% (13)	0.306	14.9% (13)	0.517
Thyroid	2.3%	(<7.0%)[a]	0.005	(<4.0%)[a]	0.455
Cardiac disease	2.0%	14.4% (20)	<0.001	(<6.0%)[a]	0.028
Stroke	0.8%	9.4% (13)	<0.001	(<9.0%)[a]	<0.001
High serum cholesterol	18.9%	33.1% (46)	<0.001	37.9% (33)	<0.001
High blood pressure	12.6%	36.0% (50)	<0.001	21.8% (19)	0.015
Obstructive sleep apnea	4.5%	15.8% (22)	<0.001	11.5% (10)	0.006

[a]Based on Department of Veterans Affairs reporting guidelines, sample numbers for groups of 11 or fewer are not presented.

vs. later) was not available, they were not assessed as risk factors for ALS; associations with these comorbidities are reported.

Statistical Analysis

We first described the prevalence of ALS in the Post-9/11 Veteran population by TBI status and the major military occupations during military service. We identified differences in the demographic and clinical characteristics among the cases and controls using the chi-square test statistic. We then used logistic regression models to determine the extent to which TBI and occupational characteristics were associated with ALS controlling for demographic characteristics and comorbidities of interest. We also described the cumulative incidence functions and hazard ratios using Cox regression analysis in the subsample of definite ALS case ($n = 139$) using the first study year in which the ICD-9 code for ALS was identified in VHA data as proxy for time and age of diagnosis.

RESULTS

A total of 226 cases of ALS were identified from the cohort over the 14-year study period. One hundred thirty nine were categorized as "Definite ALS," 87 were classified as "Possible ALS," and 20 individuals who met criteria for other ALS described above were excluded (see Supplementary Table S1).

Table I describes the demographic and clinical characteristics of the study groups. Mean age at entry to VHA for cases was significantly higher compared to those of controls. There were significant differences in demographic characteristics between definite cases of ALS and controls, with definite cases being more likely to be male and white. Definite ALS cases were also more likely to be (1) highly educated, (2) in the Air Force, (3) officers/warrant officers, and (4) Reserve/Guard compared to those with possible or no ALS. No significant demographic differences were observed between the possible ALS and no ALS groups. Depression, obstructive sleep apnea, cardiac disease, cerebrovascular disease, high cholesterol, and high blood pressure were more prevalent among both case groups compared to controls (see Table I). Diabetes and cancer were also more prevalent among the definite cases of ALS compared to controls. Proportions of those with TBI, PTSD, obesity, thyroid disease, and nicotine dependence were similar across all study groups.

Figure 1 shows the ALS prevalence over the 14-year study period (definite and possible cases combined) by TBI status, military branch of service, and occupational categories. Prevalence of ALS was similar among those with and without TBI. ALS prevalence was highest (33.2 per 100,000) among Air Force personnel and lowest (4.4 per 100,000) among marines compared to those in Army and Navy/Coast Guard. By major DoD occupational category, tactical operations officers (eg, pilots, air craft crews, and missile combat operations staff officers) had significantly higher ALS prevalence compared to administrators (administration and management officers) and general officers (all officers of General/Flag rank and all commanders, directors, and planners), Supply and Service officers and handlers, communications and intelligence specialists, and electronic/electrical/mechanical equipment repairers.

Multivariable logistic regression models with definite or possible ALS as outcome and adjusting for age, demographic characteristics, and clinical comorbidities are shown in Table II. We found that the odds of having ALS was 2.2 times more likely among tactical operations officers compared to administrators and general officers, while there was no significant difference for TBI. Other demographic characteristics and comorbidities associated with significantly higher odds of ALS were male sex, Caucasian race, depression, obstructive sleep apnea, cancer, cardiac disease, cerebrovascular disease, and high blood pressure. Entry to VHA at age below 45 years and obesity are associated with 50% lower odds of ALS.

Figure 2 shows the cumulative incidence function curves by TBI status and by the military branch of service for definite ALS cases, over the years of follow-up since entry to VHA care. Gray's test for equality of cumulative incidence functions across various military branch of services was significant with a P-value of <0.001, suggesting a significant difference in the cumulative incidence function of ALS between the branches of service. Cumulative incidence was highest for Air Force and lowest for the Marines at any given follow-up time. The hazard ratio (HR) for ALS was 1.7 (95% CI: 1.1–2.7) among those who served in the Air Force compared to those in Army, while the hazard for Marines was significantly lower [HR (95% CI): 0.3 (0.1–0.8)]. Cumulative incidence functions did not vary by TBI status over the years of follow-up.

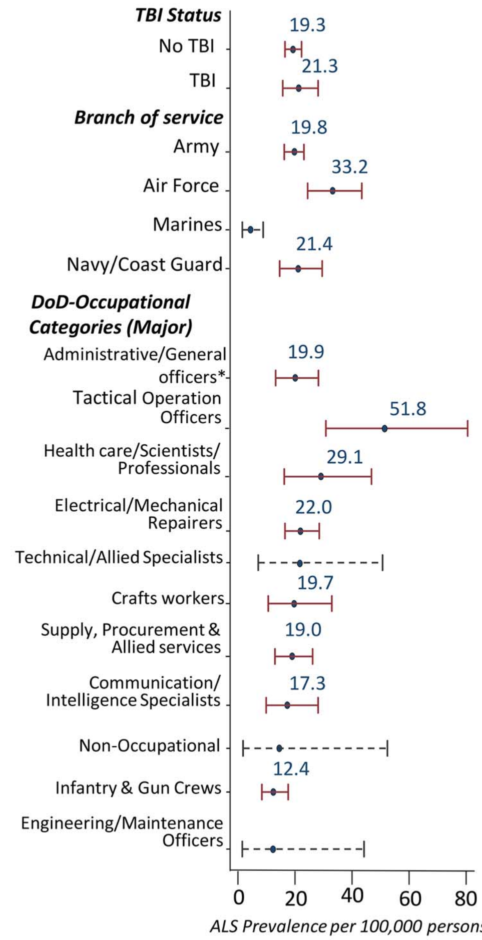

FIGURE 1. ALS prevalence (per 100,000 persons with 95% CI) over the study period FY2002–FY2015 by TBI status, branch of service, and major DoD occupational categories. Prevalence for categories with less than 10 cases of ALS was not reported and the 95% CI is represented with dashed lines.

Table II shows ALS hazard ratios for TBI and for various DoD occupational categories from various Cox regression analysis models with definite ALS as outcome. Hazard of having definite ALS was significantly higher among tactical operations officers and among the occupational category that includes health care workers, scientists, and professionals even after adjusting for demographic variables and comorbidities. Age 45 and above at entry to VHA, male sex, and white race were significantly associated with increased hazard for definite ALS. Comorbidities such as depression, cardio and cerebrovascular diseases, high blood pressure, and obstructive sleep apnea were all significantly associated with definite ALS. No significant association was noted between TBI and diagnosis with definite ALS.

DISCUSSION

This case-control study is the first to examine the prevalence of ALS among the population of U.S. Veterans deployed in support of the Post-9/11 conflicts. Although previous literature has identified military service as a risk factor for ALS,

TABLE II. Logistic Regression (Definite or Possible ALS) and Cox Regression (Definite ALS Only) Estimates for Military Occupation Characteristics, TBI, and Other Comorbidities Associated With ALS

	Definite or Possible ALS ($n = 226$) [Logistic regression aOR (95% CI)]		Definite ALS Only ($n = 139$) [Cox Regression HR (95% CI)]	
Variable	Model 1	Model 2	Model 1	Model 2
TBI (Ref: No TBI)	1.4 (1.0–1.9)	1.0 (0.7–1.4)	1.3 (0.9–2.0)	1.0 (0.6–1.6)
Primary military occupation (Ref: Administrators, general officers, and executives)				
Tactical operations officers (pilots, aircraft crew, missile, and combat operation staff)	**2.2 (1.2–3.9)**	**2.2 (1.2–3.9)**	**2.6 (1.3–5.3)**	**2.3 (1.1–4.7)**
Health care workers, scientists, and professionals	1.3 (0.7–2.5)	1.3 (0.7–2.4)	**2.2 (1.1–4.2)**	**2.0 (1.1–4.0)**
Infantry, gun crew, and seamanship	0.7 (0.4–1.2)	0.6 (0.4–1.1)	0.6 (0.3–1.2)	0.5 (0.3–1.0)
Electronic/electric/mechanical equipment repairers	1.2 (0.8–1.9)	1.1 (0.7–1.7)	1.1 (0.6–1.9)	0.9 (0.5–1.6)
Technical and allied specialists	1.2 (0.5–3.1)	1.1 (0.4–2.8)	1.6 (0.5–4.7)	1.3 (0.4–3.8)
Craft workers	1.1 (0.6–2.0)	0.9 (0.5–1.7)	0.7 (0.3–1.7)	0.6 (0.2–1.4)
Supply, procurement, and supply handlers and officers	1.0 (0.6–1.7)	0.9 (0.6–1.5)	1.1 (0.6–2.0)	1.0 (0.5–1.8)
Intelligence and communications officers	1.0 (0.5–1.8)	0.9 (0.5–1.7)	0.8 (0.4–1.9)	0.7 (0.3–1.7)
Nonoccupational (patients, students, trainees)	0.9 (0.2–3.7)	0.9 (0.2–3.8)	0.8 (0.1–5.7)	0.7 (0.1–5.2)
Engineering and maintenance	0.5 (0.1–2.1)	0.5 (0.1–2.0)	0.4 (0.1–3.0)	0.3 (0.1–2.6)
Unknown	0.6 (0.1–4.4)	0.6 (0.1–4.6)		
Age at entry to VA <45 years (Ref: ≥45 years)	**0.3 (0.2–0.5)**	**0.5 (0.4–0.8)**	**0.3 (0.2–0.4)**	**0.5 (0.3–0.7)**
Male sex (Ref: Female)		**2.0 (1.1–3.5)**		**4.0 (1.6–9.9)**
White race (Ref: Other Races)		**1.4 (1.1–1.9)**		**1.7 (1.1–2.5)**
Active military (Ref: Reserves/National Guard)		0.9 (0.6–1.2)		1.1 (0.8–1.5)
Comorbidities (Ref: No)				
Depression		**1.7 (1.2–2.4)**		**2.0 (1.3–3.0)**
PTSD		0.8 (0.5–1.1)		**0.6 (0.4–0.9)**
Cardiac disease		**3.0 (1.9–4.7)**		**3.4 (2.0–5.8)**
Cerebrovascular disease		**5.4 (3.3–8.9)**		**4.5 (2.4–8.5)**
High blood pressure		**1.8 (1.3–2.5)**		**2.3 (1.5–3.5)**
Cancer		**2.1 (1.1–4.1)**		2.1 (1.0–4.5)
Obstructive sleep apnea		**2.2 (1.5–3.4)**		**2.5 (1.5–4.2)**
Obesity		**0.5 (0.3–0.7)**		**0.3 (0.2–0.6)**
Diabetes		0.9 (0.5–1.5)		1.0 (0.5–1.9)
High blood cholesterol		1.3 (0.9–1.8)		0.8 (0.5–1.2)
Thyroid disease		1.5 (0.8–2.6)		1.7 (0.8–3.4)
Nicotine dependence		1.0 (0.7–1.4)		1.0 (0.7–1.5)

Notes. Model 1, adjusted for age at entry to VA; Model 2, adjusted for age at entry to VA, sex, race, military component, and comorbidities. Branch of service and rank were not included in the multivariate regression models as the categorization of the military occupations was based on the individual's primary Military Occupation Specialty code, branch of service, and rank. *Abbreviations:* aOR, adjusted odds ratio.

our study is the first to provide estimates by major DoD occupational categories. During the study period (FY2002–2015), the prevalence of ALS was 19.7 per 100,000 persons over 14 years, which is significantly higher given the 10-year post war ALS prevalence reported among deployed GWV and the prevalence estimates reported by ASTDR using the National ALS Registry.[3,16] We also found that among the service branches the cumulative incidence of definite ALS was significantly higher among those who served in Air Force and the DoD occupational categories of the tactical operation officers and health care workers were associated with higher risk of having ALS compared to general officers and administrators. Finally, we did not observe an association between TBI and ALS.

The prevalence of 19.7 per 100,000 persons over 14 years in our study is significantly higher than that reported for deployed GWV, which was 5.8 per 100,000 over 10 years after the Gulf War.[3] However, the two studies differed significantly in their sample characteristics and years of follow-up, and hence, the results should be compared with caution. Compared to the GWV study, our sample of deployed Post-9/11 U.S. war Veterans are relatively older (9% with age ≥45 years at the time of entry to VHA compared to <2.0% among the GWV cohort analysis). Since increasing age is associated with increased risk for ALS, this may explain a higher prevalence rate among our study population compared to GWV. Also, compared to GWV study population, our study sample consisted of significantly higher proportion of Reserves/National Guard.

Our findings also indicate a higher estimated prevalence than that reported by ATSDR using National ALS Registry for age group of <60 years (11.5 per 100,000 persons in

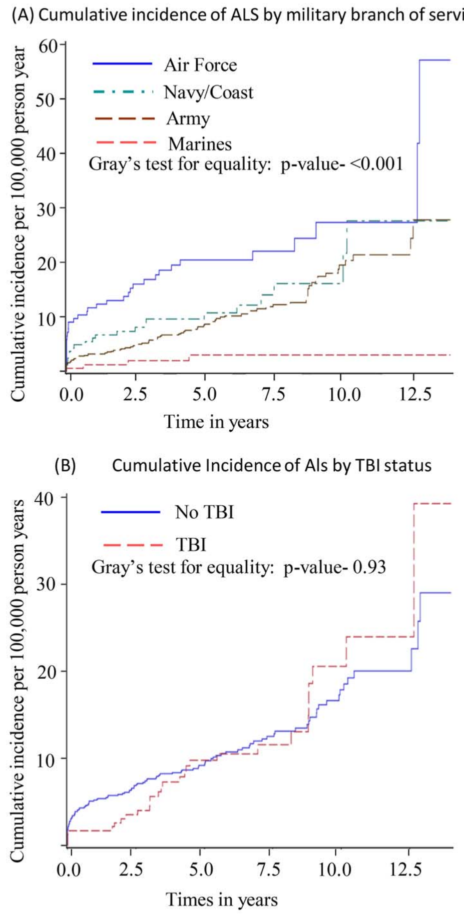

FIGURE 2. Cumulative incidence function curves of definite ALS ($n = 139$) among Post-9/11 deployed U.S. war Veterans for FY2002–FY2015 (A) by military branch of service and (B) by TBI status.

2015);[7] however, our findings may not be comparable due to methodological and cohort characteristics. National ALS Registry identifies cases from Medicare, VHA, and VBA national databases and through web portal, which enables ALS individuals to register and complete a risk factor survey. Of those who completed the risk factor survey, 23.5% self-reported having served in the military and the registry do not report ALS prevalence by military or occupational categories. Our sample, which is only based on VHA and VBA data, is a high-risk population for ALS as they are predominantly male (87.6% vs. 61.5% in registry), have military history, and were deployed—all of which are risk factors for ALS. However, it should be noted that our study cohort is relatively much younger with a mean age of 31.7 years and that 99% of ALS cases identified in our cohort were under 60 years of age, compared to those registered to the National ALS Registry where only 36% of cases reported were <60 years of age.[16] Future studies are required to examine if there is an early onset of ALS among this high-risk population.

Similar to the findings among the GWV reported by Horner et al.,[3] the prevalence of ALS among Air Force personnel (35.1 per 100,000 over 14 years) was significantly higher compared to Army and Marine personnel. This was also consistent with ALS being reported to be the only noncancer disease found to contribute significantly to excess mortality (proportional mortality ratio 2.4; 95% CI: 1.0–4.6) among U.S. civilian pilots and navigators.[20] The lower prevalence rate of ALS among Marines in our study was also consistent with the lower risk of ALS among marines previously reported.[3,5]

Tactical operations officers' study category consisted primarily of pilots, aircraft crew, missile, and combat operations staff and included personnel from across all branches of services (62% from Army, 15% from Air Force, 13% Navy/Coast Guard, and 10% Marines). Our finding of high risk for ALS among tactical operations officers compared to general officers and administrators suggests the need for evaluating the role of occupational exposures these personnel are exposed to, such as ionizing radiation, electromagnetic fields, ozone, jet emissions, noise etc., in the pathogenesis of ALS. Electromagnetic fields, high-intensity radar waves, diesel exhaust, and electric shock have been previously reported to be risk factors for ALS.[6,21–23] A combination of exposures to electromagnetic fields, high-intensity radar waves, and engine exhaust may be a possible explanation for the increased risk among the Air Force personnel and the tactical operations officers and should further be explored using environmental exposure data. Recent meta-analysis studies have shown slightly increased risk of ALS in those exposed to higher levels of extremely low frequency magnetic fields, and flight crews are exposed to elevated levels of magnetic field generated by the aircraft's electrical system.[24–29] Similar to that reported in the literature, health care workers in our study population were also at increased risk for ALS and may represent earlier diagnosis or better access to care among these.[22]

Our study found that TBI, both independently and when adjusted for other covariates, was not associated with a diagnosis of ALS. Although head trauma has been linked to increased risk for a variety of neurodegenerative diseases,[10,30] recent studies suggest that only repetitive TBI and not moderate-to-severe TBI is associated with ALS and other neurodegenerative diseases.[31,32] However, most of these studies were in civilian samples with heterogeneity in the mechanisms of injury, which may differ significantly in military populations.[33] Our measure of TBI is based on diagnosis codes documented in VHA care, with no ability to identify repetitive TBI or over the lifetime of the Veteran and TBI due to neuromuscular conditions inherent in the onset of ALS. Thus, our finding must be interpreted with caution.

The higher prevalence of ALS reported in this relatively younger cohort of Veterans, compared to that of studies from other civilian or national registry population,[16] suggest that deployed Veterans are at increased risk of early onset of ALS compared to other populations. The findings from this study were also consistent with the findings of early onset ALS among deployed GWV.[2,3,34] However, only 74% of ALS cases in our cohort were under the age of 45 years at the time of entry into the study compared to 98% in the GWV study. Similar to the lower age-specific ALS incidence rates observed among GWV under 45 years of age, the odds of ALS diagnosis among those who entered the VHA at age <45 years was 50% lower compared to those who entered at age ≥45 years. However, given the average age of ALS diagnosis is around 55 years, these young Veterans may be at increased risk for developing ALS as they age and should be surveilled into the future. Consistent with prior literature,[16,35] our study also found elevated risk for men and whites.

We also found an association of various psychiatric and metabolic conditions with ALS that is consistent with existing studies that identified these conditions as risk or prognostic factors in ALS.[22,36,37] Lack of data regarding the actual time of ALS diagnosis (may have occurred while in the DoD or civilian care) prevented us in evaluating these comorbidities as risk factors for ALS in this population. However, our study found that depression was highly associated with ALS, while anxiety and bipolar disorders did not show significant association. A recent study by Turner et al.,[38] which investigated the predetermining role of these conditions in ALS, also concluded that depression remains a significant remote psychiatric comorbidity 5 years prior to the onset of ALS. Significant associations of cardiac and cerebrovascular diseases, high blood pressure, and obstructive sleep apnea with ALS found in our study are also consistent with the findings in the literature.[39–43]Diabetes was not associated with ALS in our study and the odds of having obesity was significantly less likely among those with ALS. This is consistent with studies by Scarmeas et al. and O'Reilly et al., which reported that ALS rates were significantly lower among obese subjects, and a recent Denmark study, which concluded type II diabetes a protective factor for ALS and other neurodegenerative diseases.[37,44,45]. The positive association of ALS with cancer in our study is consistent with a Swedish study, which reported an increased risk of ALS during the first year after cancer diagnosis.[46] However, recent studies have reported a potential inverse relationship between neurodegenerative diseases and cancer.[46–48] Thus, the role of cancer and ALS in this veteran population requires further investigation regarding the type of cancer and its association with ALS.

Major limitation to this study is lack of information regarding type of ALS, that is, familial vs. sporadic. About 90% to 95% of ALS cases are sporadic; however, longitudinal epidemiological studies indicate that combination of various environmental exposures and a genetic predisposition increases the nerve cell disease burden so that the ALS disease process starts.[49–51] Family history data or genetic testing information are not available in the VA or DoD administrative databases. However, the results of this study can serve as hypothesis generator for future studies to examine the environmental exposures among Veterans with a family history of ALS or with family members who served the military in the past. Our study relied on administrative VA data to examine prevalence among deployed Post-9/11 U.S. war Veterans. Although this approach allowed a larger and less random sample compared to previous studies, the clinical diagnosis was not confirmed, and it is challenging to directly compare the data to previous reports. The DoD occupational code used in this study is only representative of individual's primary occupation during the military service and may not be an accurate measure of lifetime occupational exposure.

Although we based our case definitions on the ATSDR's updated algorithm from defining ALS cases, due to lack of access to Medicare and death certificate data, we categorized the individual who only have a VBA code of 8017 (ie, who received VHA benefits for ALS but no VHA care) as possible cases and were included in the analysis. This may have led to some misclassification bias. However, results were similar for the analysis including both definite and possible ALS cases vs. analysis including definite ALS cases alone. Data regarding the age or year of diagnosis could not be determined from this administrative data, and some Veterans might have had their ALS diagnosis prior to the entry to the VHA for which the data were not available. For the Cox regression analysis of definite ALS cases in this study, the year in which the first ICD-9 code for ALS was identified in VHA data was considered as a proxy for the time and age of diagnosis. Hence, the cumulative incidence rates presented should be interpreted with a caution. But given the full range of health care benefits VHA offers to these disabled Veterans and the low average survival time from the disease, this proxy variable for time of diagnosis obtained from the VHA data may not be far from the true time of diagnosis.

The temporal relationship between ALS diagnosis and comorbid conditions included in our analysis could not be reliably determined; hence our analysis could not examine these comorbidities from the lens of a risk factor. However, our results are consistent with prior risk factor studies and as such contribute to our understanding of disease burden in Veterans with ALS. Finally, the results of our study can be reasonably generalized to the deployed Veteran population but may not be comparable to findings from the National ALS Registry and civilian. Strengths of this study include a long study period, bigger sample population, and access to data from various administrative databases.

In conclusion, our results show a greater prevalence of ALS among the Post-9/11 deployed U.S. war Veterans and at a relatively younger age, with individuals in DoD occupational categories of tactical operations officers and health care workers being at highest risk. Future studies are needed to confirm the ALS risk among the independent military occupations by examining exposures specific to these occupations that are associated with ALS. Furthermore, there is a need for future ALS surveillance measures in this population as more cases of ALS may develop with the aging of this cohort. Research examining military risk factors and occupational exposures that lead to early onset of ALS is needed to determine if occupational safety approaches can reduce risk for this terminal disease. The profound comorbidity revealed in our cohort also indicate the multiple effects of ALS, which necessitate an interdisciplinary team for the delivery of a comprehensive, well-planned approach to care. These findings further support VHA's commitment to care of these service-connected disabled Veterans through a National ALS System of Care with a mission to address and manage the multiple medical, physical, functional, psychological, and social effects of ALS.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *MILMED* online.

FUNDING

VA Health Services Research and Development Service (Grant no. DHI 09-237). VA Clinical Sciences Research and Development (Grant no. I01 CX001246). VA Health Services Research and Development Service grant (Grant no. RCS 17-297).

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